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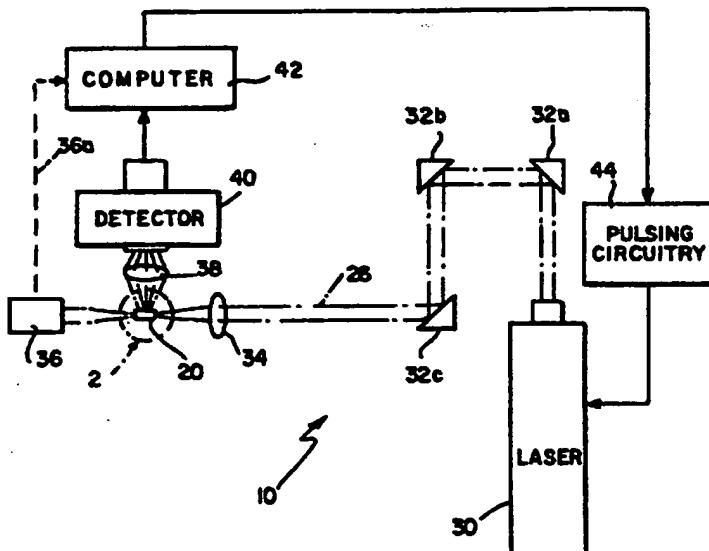
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(54) Title: METHOD AND APPARATUS FOR NON-DESTRUCTIVE ELEMENTAL ANALYSIS OF THE HEADSPACE OF A SEALED CONTAINER



(57) Abstract

A method and apparatus (10) is provided for detecting the elemental composition of the headspace (24) of a sealed container (20). The apparatus (10) includes a laser (30) capable of being pulsed (44) and creating a plasma within the headspace (24) and a detector (40) for collecting the atomic emission generated by the plasma, wherein the intensity of the emission detected from each element is proportional to its volumetric concentration within the headspace (24). This apparatus (10) is particularly useful for detecting the presence of oxygen contamination within the headspace (24) of a hermetically sealed pharmaceutical vial (20, 27) wherein the vial contents (22) were sealed under a nitrogen atmosphere and are susceptible to oxygen contamination.

METHOD AND APPARATUS FOR NON-DESTRUCTIVE ELEMENTAL  
ANALYSIS OF THE HEADSPACE OF A SEALED CONTAINER

Field of the Invention

5 This invention relates, in general, to a method and apparatus for detecting the elemental composition of the headspace of a sealed container, and, more specifically, to a method and apparatus for non-destructively measuring the 10 oxygen content in the headspace of a hermetically sealed pharmaceutical vial containing a pharmaceutical solution susceptible to contamination in the presence of oxygen.

Background of the Invention

15 A variety of processed products are packaged and shipped in individual hermetically sealed containers to prevent contamination by such external sources as air and moisture. However, unless the purity or integrity of such a product can be ascertained visually, the only known methods for testing product integrity involve invasive or 20 destructive procedures. Thus, the product testing procedure itself can lead to product contamination. For this reason, various statistical methods for determining product integrity have been developed, wherein only a statistically significant number of containers are 25 invasively or destructively tested. If this statistically significant number of containers is found to contain uncontaminated product, then the entire production lot is estimated to be uncontaminated within a predetermined error. Obviously, this type of procedure results in wasted 30 product and less than 100 percent accuracy in determining contaminated product.

35 In some industries this waste is de minimis and the error is tolerable. However, in other industries, such as the pharmaceutical industry for example, this waste may be extremely expensive and the error intolerable. For

instance, contaminated pharmaceutical products may result in a variety of detriments ranging from a reduced potency product to a potentially life-threatening product, depending on the type of product and contaminant involved.

5       As a specific example, drugs such as Human Growth Hormone, Vancomycin and Dobutrex are stored in vials in the presence of nitrogen. If, for whatever reason, outside air is allowed to enter into the headspace of such a vial, oxygen present in the air will begin to break down the drug  
10      and decrease its potency. Presently, two methods of testing this type of product's integrity are used. The first method involves the aforementioned statistical sampling. The second method involves the use of Raman Spectroscopy techniques which, although non-destructive,  
15      are slow, expensive and generally too cumbersome to integrate into a production environment. The ideal solution to such a problem is a time-efficient and non-destructive method of determining product integrity wherein up to 100 percent of a production lot may be tested to  
20      screen for contaminated product.

It is generally known that high-intensity laser radiation can be focused onto a medium to provide a power density sufficient to induce an optical plasma. The characteristic atomic emission from the excited species of  
25      the medium may then be detected by a photoelectric detector, for example, and then further processed to provide spectral map of the medium. Since the intensity of each element on the spectral map is proportional to its concentration within the medium, such a system is useful in  
30      determining the elemental composition of the medium.

Systems utilizing these concepts for the elemental analysis of liquid samples are disclosed in U.S. Patent Nos. 4,561,777 and 4,925,307. Similar systems for the elemental analysis of solid samples are disclosed in V.  
35      Majidi et al., Analytical Chemistry, vol. 63, no. 15, 1991,

p. 1600 and D. K. Ottesen et al., Applied Spectroscopy, vol. 46, no. 6, 1989, p. 967. Still other systems for the elemental analysis of aerosols are disclosed in L. J. Radziemski et al., Analytical Chemistry, vol. 55, no. 8, 5 1983, p. 1246 and W. L. Flower et al. (unpublished). Finally, an overview of optically induced plasma and their applications is given in V. Majidi, Spectroscopy, vol 8, no. 3, 1993, p. 16.

Thus far, the above-described concepts have not been 10 applied to the elemental analysis of the headspace of a sealed container. However, provided the container is optically accessible, an optical plasma can be induced in the headspace, and the resulting spectral emission analyzed, in a non-destructive manner and in a production 15 environment.

#### Summary of the Invention

According to one aspect of the present invention, an apparatus for non-destructively analyzing the elemental 20 composition of the headspace of a sealed container containing a product is provided. This embodiment includes an optically accessible container containing the product wherein the container is sealed and has a volumetric capacity in excess of the volume of the product contained 25 therein. This excess volume defines the headspace. The apparatus further includes a laser for generating pulsed electromagnetic radiation having sufficient intensity to induce a plasma within the headspace. This plasma generates an atomic emission from each element contained 30 within the volume of the induced plasma. Finally, the apparatus includes means for detecting the atomic emission, wherein the intensity of the emission detected from each element is proportional to its volumetric concentration within the headspace.

35 According to another aspect of the present invention,

an apparatus for non-destructively measuring the concentration of at least one specific element in the headspace of a hermetically sealed pharmaceutical vial containing a pharmaceutical solution is provided. As with 5 the previous embodiment, this apparatus includes an optically accessible pharmaceutical vial containing the solution wherein the vial is hermetically sealed and has a volumetric capacity in excess of the volume of the solution contained therein. This excess volume defines the 10 headspace. The apparatus further includes a laser for generating repetitively pulsed electromagnetic radiation having sufficient intensity to induce a plasma within the headspace. This plasma generates an atomic emission from each element contained within the volume of the induced 15 plasma. Finally, means are provided for detecting the atomic emission, wherein the intensity of the emission detected from the specific element is proportional to its volumetric concentration within the headspace.

According to yet another aspect of the present 20 invention, a method is provided for non-destructively analyzing the elemental composition of the headspace of a sealed container containing a product. This method includes the steps of: a.) providing an optically accessible sealed container containing the product wherein 25 the container has a volumetric capacity in excess of the volume of the solution contained therein, the excess volume defining the headspace, b.) inducing a plasma within the headspace to generate an atomic emission from each element contained therein, and c.) detecting the atomic emission, 30 wherein the intensity of the emission detected from each element contained within the headspace is proportional to its volumetric concentration within the headspace.

#### Brief Description of the Drawings

35 FIG. 1 is a schematic representation of an apparatus

for non-destructively analyzing the elemental composition of the headspace of a sealed container containing a product, according to the present invention.

FIG. 2 is a magnified view of the container shown in 5 the circled region 2 of FIG. 1.

FIG. 3 is the time-resolved atomic emission signal of an optical plasma induced in the headspace of a typical sealed pharmaceutical vial, using the apparatus of FIG. 1.

FIG. 4 is a wavelength-resolved spectrum of an optical 10 plasma induced in the headspace of a pharmaceutical vial sealed under a nitrogen atmosphere and contaminated with oxygen.

FIG. 5 is a laser plasma calibration curve for various known amounts of oxygen and nitrogen in a sealed container.

15 FIG. 6 is a laser plasma calibration curve similar to FIG. 5, but for lower concentrations of oxygen.

#### Description of the Preferred Embodiment

For the purposes of promoting an understanding of the 20 principles of the invention, reference will now be made to the embodiment illustrated in the drawings and specific language will be used to describe the same. It will nevertheless be understood that no limitation of the scope of the invention is thereby intended, such alterations and 25 further modifications in the illustrated device, and such further applications of the principles of the invention as illustrated therein being contemplated as would normally occur to one skilled in the art to which the invention relates.

30 Referring now to FIG. 1, an apparatus 10 for detecting the elemental composition of the headspace of a sealed container containing a product is shown. A sealed container 20 is shown disposed in the path of a laser beam 26 generated by a laser 30. FIG. 2 shows a magnified view 35 of the sealed container 20 located in the circled region 2

of FIG. 1. The headspace 24 is defined as the excess volume of the container 20 located between the volume of the product 22 contained therein and the sealed end 28, formed by end cap 27. The container 20 must be optically 5 accessible, meaning that it is to be constructed of any material that does not absorb radiation at the laser wave length or at the wave length of the spectral window of interest (more fully described hereinafter). In a preferred embodiment, the closed container comprises a 10 hermetically sealed glass vial commonly known in the pharmaceutical industry.

The laser beam 26, generated by the laser 30, is directed by mirrors 32a, 32b, and 32c to a focusing lens 34. Focusing lens 34 serves to focus the laser beam 26 15 from the laser 30 to an appropriate spot size within the container 20. An optical component 36 receives the portion of the laser beam 26 passing through the headspace 24 of the container 20, and may perform a variety of desired functions. In one embodiment, component 36 is a 20 simultaneous wavelength calibration device such as a hollow-cathode lamp or other wavelength calibration mechanism. In this embodiment, the component 36 is connected, via the broken line 36a, to the computer 42 so that wavelength calibration can be effectuated by known 25 methods. In another embodiment, component 36 is a beam stop and requires no external connection.

It is generally known that an optically induced plasma (or laser-induced plasma) can be generated by focusing the output of a pulsed laser onto a small spot. The breakdown 30 threshold is defined as the minimum optical power density required to form a plasma. Although different materials and mediums have different breakdown threshold values, an optical plasma is produced when the laser power density exceeds several megawatts per centimeter<sup>2</sup>. The crucial 35 factor for the formation of a laser plasma is the magnitude

of the optical power per unit area. Thus, to improve the laser power density, one must either increase the optical power delivered by the laser or reduce the area onto which the laser beam is focused. For a laser beam with a 5 Gaussian propagation, the effective radius of the focused beam ( $\omega_0$ ) is given by:

$$\omega_0 = \frac{\lambda f}{\pi \omega_1}$$

where  $\lambda$  is the wavelength of the laser 30,  $\omega_1$  is the radius 10 of the unfocused laser beam 26, and  $f$  is the focal length of the focusing lens 34. It is known in laser plasma spectroscopy to focus the spot size of a laser beam to achieve extremely high peak power densities, which in turn yield higher excitation temperatures. The requirements for 15 the laser 30 are therefore dependent on the ability to achieve a small focused beam radius  $\omega_0$  as well as the breakdown threshold value of the contents of the headspace 24 of the container 20. In a preferred embodiment, an Nd:YAG laser is used with a focusing lens 34 having a focal 20 length of between approximately 10.0-15.0 mm.

The characteristic atomic emission from the excited species within the volume of the optically induced plasma are collected and transferred to a detector 40. In a preferred embodiment, an imaging lens 38 is used to collect 25 and transfer the atomic emission. However, the present invention contemplates utilizing other known methods of accomplishing the collection and transfer of the atomic emission such as, for example, a fiber optic imaging system. Although analytical signals generated by laser 30 plasmas can be collected with devices based on acoustical, electrical, mass, or photoelectric detection schemes, photoelectric devices are the preferred detectors for evaluation of atomic emission from laser-induced plasmas. The plasma-induced atomic emission is ultimately detected 35 by either a photomultiplier tube or a photodiode array (not shown) contained within detector 40. Detector 40 then

converts the atomic emission into electrical signals which are received by computer 42 for further processing.

Computer 42 also controls pulsing circuitry 44 which is connected to laser 30 for providing controlled pulses of

5 the laser beam 26.

When a plasma is formed by a pulsed laser, the emission from the excited species is transient in nature. Thus, when the laser pulse is terminated, electrons decelerate and a massive continuum emission is observed.

10 This continuum is predominately due to Bremsstrahlung emission and ion-electron recombination. A few hundred nanoseconds later, the atomic line emission becomes the dominant spectral feature. The phenomenon is shown in FIG. 3. Because of the manner in which the plasma cools, only  
15 atomic emissions are discernible during the latter part of the plasma lifetime (up to 10's of microseconds). Although signals resulting from detector 40 may be evaluated in either time-resolved or time-integrated modes, excited species are observed, in the preferred embodiment, in the  
20 time-resolved mode due to the extended atomic emission lifetime. As shown in FIG. 3, emission line 50 represents the continuum emission near the atomic transition while emission line 52 represents the background-corrected atomic emission of the elemental composition of the headspace 24  
25 of container 20. While atomic emission is easily detectable up to 50 microseconds after the plasma onset, background emission intensity is reduced significantly during the first microsecond. An optimum analytical signal is achieved when the background emission is low and the  
30 signal magnitude is relatively high. Selection of the best observation time window is thus a balance between these two factors.

Because the formation of optical plasmas does not require any mechanical power transfer or energy coupling  
35 elements, laser plasmas can be generated in any optically

accessible medium. If the medium contains an analyte, the emission from that analyte is proportional to its concentration within the medium. Thus, if an analyte is present within headspace 24 of vial 20, its concentration 5 within the head space can be determined using the apparatus 10 of FIG. 1.

To facilitate the understanding of the present invention, a specific example is provided. In the pharmaceutical industry, liquid pharmaceuticals such as 10 Human Growth Hormone (HGH), Vancomycin, and Dobutrex, are hermetically sealed in glass vials under a nitrogen atmosphere. For these types of pharmaceuticals, as well as many others, oxygen is considered a contaminant since it breaks down the pharmaceutical and thereby reduces its 15 potency. Thus, pharmaceuticals that are susceptible to oxygen contamination are hermetically sealed in vials in which the headspace ideally contains purely nitrogen. If, in the production facility, a hermetic seal is broken and a predetermined threshold level of oxygen is allowed to enter 20 the headspace, the vial should be considered contaminated and thereafter scrapped. With the specific pharmaceutical examples given above, vials containing as low as 1% oxygen within the headspace should be considered contaminated. In order to effectively screen for such contamination, the 25 apparatus 10 of FIG. 1 may be integrated into a production line to screen 100% of the sealed vials.

Through experimentation, it has been determined that the fundamental output of a Nd:YAG laser can be utilized to form a plasma inside of a sealed pharmaceutical vial 30 without any damage to the glass container. Furthermore, as shown in FIG. 4, a spectral region has been located where atomic emission lines from both nitrogen and oxygen are present at wavelengths that can be transmitted through the glass vials. FIG. 4 thus represents a spectral window 35 where both oxygen lines 60 and nitrogen lines 62 are

present.

In determining the concentration of oxygen in a nitrogen atmosphere, absolute emission intensities of the two species is not a particularly useful parameter.

5 Rather, for quantitative purposes, much more precise results can be obtained by ratioing the intensities of the two known species. In the present invention, this is accomplished by comparing this ratio from any vial with a laser plasma calibration curve for oxygen concentration in  
10 the presence of nitrogen as shown in FIG. 5. From FIG. 5, it is seen that the calibration curve loses significant linearity below approximately 0.5% oxygen and above approximately 12.0% oxygen. When this same data is plotted for a lower concentration range, as shown in FIG. 6, a  
15 linear calibration curve is obtained. A linear equation obtained from this plot can then be used in the subsequent analysis to quantitatively estimate the concentration of oxygen in the various bottles. In many instances, however, this quantitative information is not as useful as  
20 determining whether the oxygen contamination is above a predetermined threshold. The latter case is the most useful in a production facility, and the calibration curves of either FIGS. 5 or 6 may be used to determine if the oxygen content of a particular vial has exceeded the  
25 threshold.

In a production environment, a laser capable of generating repetitively pulsed electromagnetic radiation is directed through the sealed vial or container and into the headspace. A plasma is induced within the headspace  
30 generating an atomic emission from each element contained within the volume of the induced plasma. This atomic emission is then detected within a predetermined time period after inducing the plasma in order to reduce the background emission detection. This time-resolved emission  
35 information is then converted via known software techniques

into a wavelength spectral resolution of the emission. The intensities of the various elements in the spectrum, oxygen and nitrogen in this case, are then determined and either observed for quantitative information, or ratioed and 5 compared to the calibration curve of either FIG. 5 or 6 to determine whether a threshold oxygen concentration level has been exceeded.

While the invention has been illustrated and described in detail in the drawings and foregoing description, the 10 same is to be considered as illustrative and not restrictive in character, it being understood that only the preferred embodiment has been shown and described and that all changes and modifications that come within the spirit of the invention are desired to be protected. For example, 15 the invention described herein is equally applicable when the sealed container 20 contains solids, gases and liquids other than pharmaceutical solutions.

## CLAIMS:

1. An apparatus for non-destructively analyzing the elemental composition of the headspace of a sealed container containing a product, comprising:
  - 5 an optically accessible container containing the product, said container being sealed and having a volumetric capacity in excess of the volume of the product contained therein, said excess volume defining the headspace;
  - 10 a laser for generating pulsed electromagnetic radiation having sufficient intensity to induce a plasma within the headspace, said plasma generating an atomic emission from each element contained within the volume of said induced plasma; and
  - 15 means for detecting said atomic emission, wherein the intensity of said emission detected from each element is proportional to its volumetric concentration within the headspace.
2. The apparatus of claim 1, wherein said means for detecting said atomic emission includes means for measuring the concentration of at least one specific element.
3. The apparatus of claim 1, wherein said laser is configured to permit repetitive pulsing of said electromagnetic radiation.
- 25 4. The apparatus of claim 1, wherein said means for detecting includes a photoelectric detector.
5. The apparatus of claim 2, wherein said container includes a hermetically sealed pharmaceutical container.
- 30 6. The apparatus of claim 5, wherein said pharmaceutical container includes a vial and said product includes a pharmaceutical solution.
7. The apparatus of claim 6, wherein said specific element includes oxygen.
- 35 8. The apparatus of claim 6, wherein said solution is taken from a group consisting of Human Growth Hormone,

Vancomycin, and Dobutrex.

9. An apparatus for nondestructively measuring the concentration of at least one specific element in the headspace of a hermetically sealed pharmaceutical vial containing a pharmaceutical solution, comprising:

an optically accessible pharmaceutical vial containing the solution, said vial being hermetically sealed and having a volumetric capacity in excess of the volume of the solution contained therein, said excess 10 volume defining the headspace;

a laser for generating repetitively pulsed electromagnetic radiation having sufficient intensity to induce a plasma within the headspace, said plasma generating an atomic emission from each element contained 15 within the volume of said induced plasma; and

means for detecting said atomic emission, wherein the intensity of said emission detected from the specific element is proportional to its volumetric concentration within the headspace.

20 10. The apparatus of claim 9, wherein the specific element includes oxygen.

11. The apparatus of claim 10, wherein the solution is taken from the group consisting of Human Growth Hormone, Vancomycin and Dobutrex.

25 12. A method for non-destructively analyzing the elemental composition of the headspace of a sealed container containing a product, comprising the steps of:

a. providing an optically accessible sealed container containing the product, said container having a 30 volumetric capacity in excess of the volume of the solution contained therein, said excess volume defining the headspace;

b. inducing a plasma within the headspace to generate an atomic emission from each element contained 35 therein; and

c. detecting said atomic emission,  
wherein the intensity of said emission detected  
from each element contained within the headspace is  
proportional to its volumetric concentration within the  
5 headspace.

13. The method of claim 12, wherein said inducing  
step further comprises:

(1) providing a laser capable of generating  
repetitively pulsed electromagnetic radiation; and  
10 (2) directing said radiation through the  
container and into the headspace.

14. The method of claim 13, wherein said detecting  
step further comprises:

(1) providing a photoelectric detector;  
15 (2) detecting said emission within a  
predetermined time period after inducing said plasma in  
order to reduce background emission detection;  
(3) determining the wavelength spectral  
resolution of said emission; and  
20 (4) determining the intensity of the various  
elements in said spectrum.

15. The method of claim 14, wherein the concentration  
of at least one specific element contained within the  
headspace is measured, further comprising the steps of:  
25 e. observing the intensity of the specific  
element within a spectral window in which the specific  
element is expected to be found.

16. The method of claim 15, wherein the specific  
element is capable of contaminating the product.  
30 17. The method of claim 15, wherein the sealed  
container includes a hermetically sealed pharmaceutical  
container.

35 18. The method of claim 16, wherein said  
pharmaceutical container includes a vial and the product  
includes a pharmaceutical solution.

15

19. The method of claim 16, wherein the specific element includes oxygen.
20. The method of claim 17, wherein said pharmaceutical solution is taken from a group consisting of 5 Human Growth Hormone, Vancomycin and Dobutrex.

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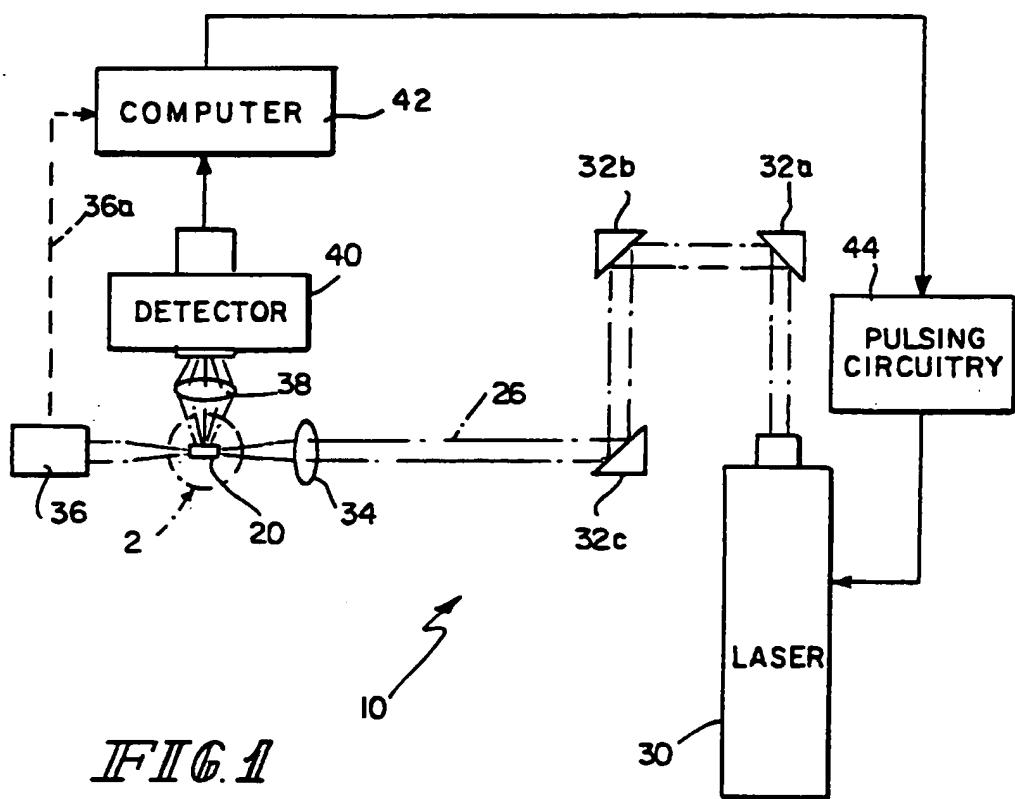


FIG. 1

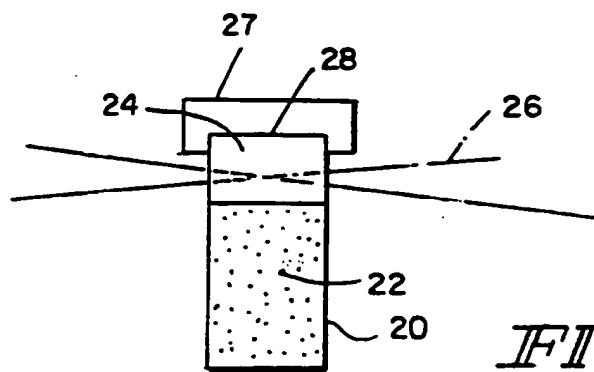
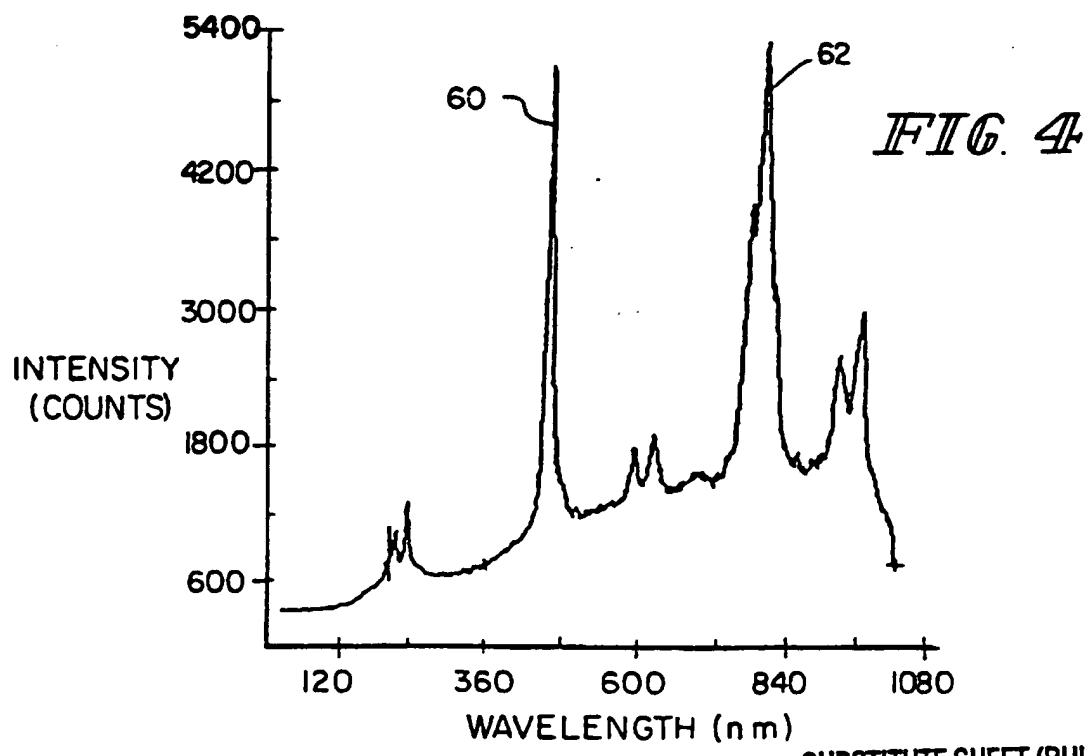
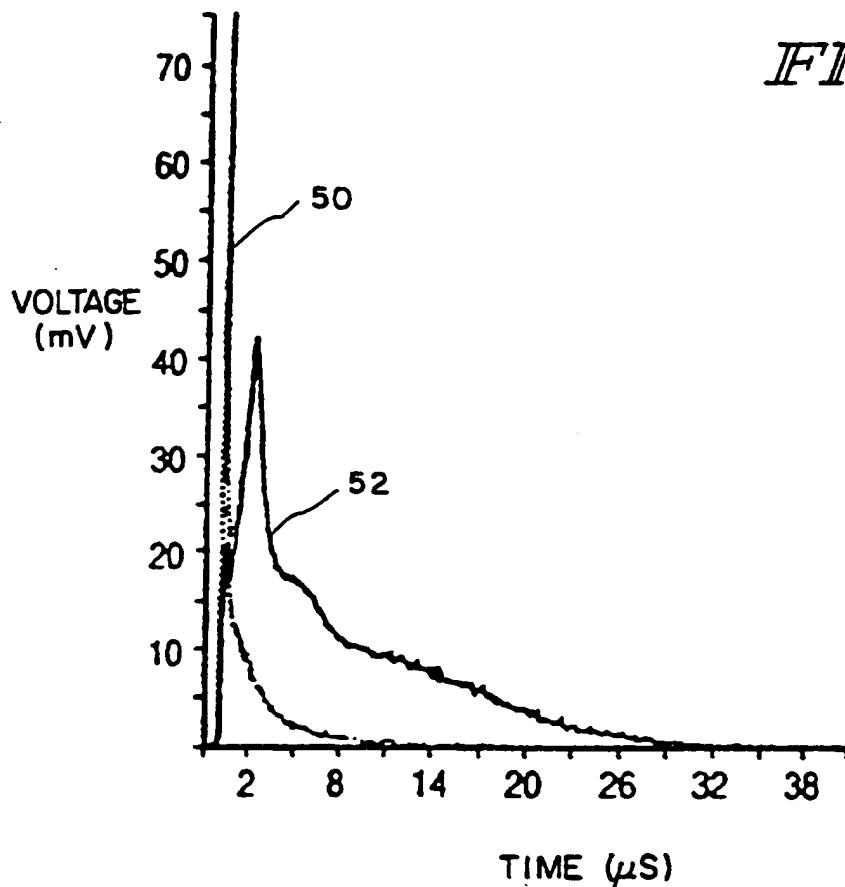


FIG. 2

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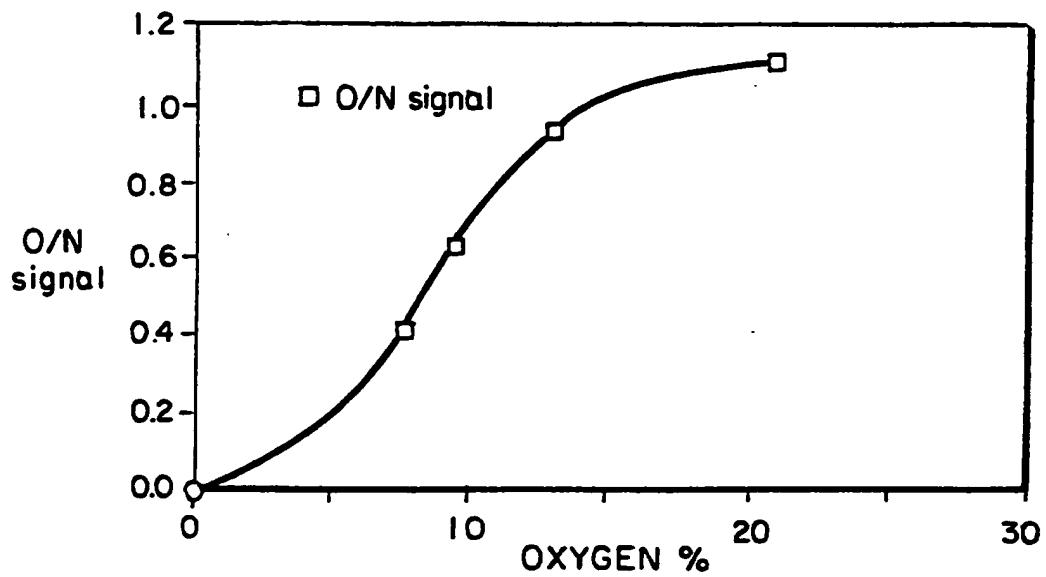


FIG. 5

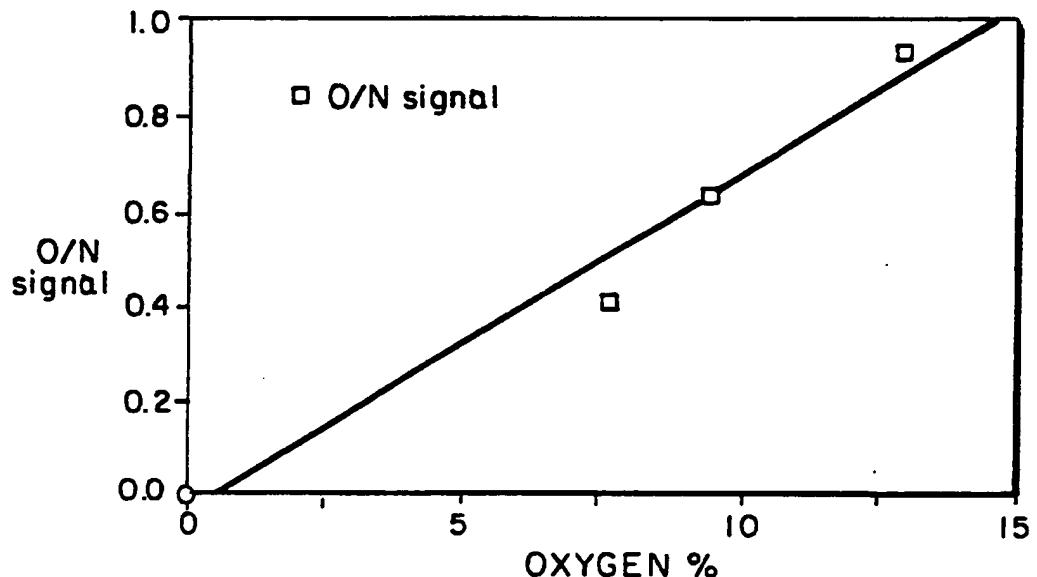


FIG. 6

# INTERNATIONAL SEARCH REPORT

International application No.  
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## A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :G01N 33/15; 21/01, 21/64

US CL :Please See Extra Sheet.

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 250/458.1, 459.1, 461.2; 356/301, 317, 318; 422/62, 83, 91; 436/136, 138, 171, 172

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

Please See Extra Sheet.

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	ANALYTICAL CHEMISTRY, Vol. 58, issued 1986, Powell et al, "Rapid Headspace Analysis In Sealed Drug Vials By Multichannel Raman Spectrometry", pages 2350-2352, see entire document.	1-20
Y	ANALYTICAL CHEMISTRY, Vol. 55, issued 1983, Radziemski et al, "Time-Resolved Laser-Induced Breakdown Spectrometry of Aerosols", pages 1246-1252, see entire document.	1-20
Y	Chemical Abstracts, Vol. 98, No. 20, issued 16 May 1983, Eliseev et al, "Study of possibilities of spontaneous Raman scattering for molecular plasma diagnostics", page 559, column 2, abstract no. 169616q, Deposited Doc., 1982, VINITI 1717-82, 20 pages, see entire abstract.	1-20

<input checked="" type="checkbox"/>	Further documents are listed in the continuation of Box C.	<input type="checkbox"/>	See patent family annex.
*A*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"E"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step
"L"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is taken alone
"O"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"Z"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"P"	document referring to an oral disclosure, use, exhibition or other means		document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
10 SEPTEMBER 1995	29 SEP 1995
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer  ARLEN SODERQUIST Telephone No. (703) 308-0196

**INTERNATIONAL SEARCH REPORT**

International application No.

PCT/US95/08914

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US, A, 4,889,992 (HOBERMAN) 26 December 1989.	1-20
A	JOURNAL OF THE PARENTERAL DRUG ASSOCIATION, Vol. 34, No. 2, issued March-April 1980, Bailey et al, "Non-Destructive Headspace Gas Analysis in Pharmaceutical Ampules by 5145 A Laser Raman Spectroscopy", pages 127-133.	1-20
A	JOURNAL OF APPLIED PHYSICS, Vol. 53, No. 2, issued February 1982, Stricker et al, "Experimental investigation of electrical breakdown in nitrogen and oxygen induced by focused laser radiation at $1.064\mu$ , pages 851-855.	1-20
A	JOURNAL OF APPLIED PHYSICS, Vol. 56, No. 7, issued 01 October 1984, DiMauro et al, "Two-photon laser-induced fluorescence monitoring of O atoms in a plasma etching environment", pages 2007-2011.	1-20
A	Chemical Abstracts, Vol. 113, No. 12, issued 17 September 1990, Bukin et al, "Use of laser spark spectroscopy for analyzing the elemental composition of aqueous media", page 777, column 2 abstract no. 108386w, Zh. Prikl. Spektrosk., 1990, 52(5), pages 736-738, see entire abstract.	1-20

**INTERNATIONAL SEARCH REPORT**

International application No.

PCT/US95/08914

**A. CLASSIFICATION OF SUBJECT MATTER:**

US CL :

250/458.1, 459.1, 461.2; 356/301, 317, 318; 422/62, 83, 91; 436/136, 138, 171, 172

**B. FIELDS SEARCHED**

Electronic data bases consulted (Name of data base and where practicable terms used):

STN (CA, MEDLINE, BIOSIS FILES) search terms: laser spark#, LIBS, laser# induc?, plasma#, breakdown , ioniz?, o2, o, oxygen, det##, detect?, determin?, measur?, monitor?, analysis, testing, pharmaceut?, medic? headspace#, head space#, fluoresc?, LIF, container#, vial#, bottle#, dissociat? recombination, post discharge, optical emission, human growth hormone, vancomycin, dobutrex, nondestruct?, nonintru?, ampul#, atom?, emission, emis?, absor?, gas##